

CELL INJURY

CELL

Cells are the basic unit of tissue, which form organs and system in the human body. Traditionally body cells are divided in two main type.

- A. Epithelial
- B. Mesenchymal cells.

Study of abnormalities in structure and function of cells in disease has remained the focus of attention in understanding of disease. Thus most forms of disease begins with cell injury followed by consequent loss of cellular function.

1. CELL INJURY

Cell injury is defined as the effect of a variety of stresses due to etiologic agents a cell encounters resulting in changes in its internal and external environment.

- Various forms of cellular responses to cell injury follows.

- cell adaptation - when there is increased functional Demand, the cell may adapt to the changes which are expressed Morphologically, which then revert back to normal after stressed removed.
- Reversible & irreversible cell injury - when the stress mild to moderate, the injured cell may be recover it is called reversible cell injury. While persistent and severe form of cell injury may cause cell death it is called irreversible injury.
- intracellular accumulations - Metabolites may accumulate within the cell

2. ETIOLOGY OF CELL INJURY

The cells may be broadly injured by Two ways.

- A. Genetic causes.
 - B. Acquired causes.
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- A. Genetic causes
 - Developmental defect
 - cytogenic defect
 - Storage disease
 - Disorder with Multifactorial inheritance.

B. Acquired causes

The acquired causes of cell injury can be further categorised as under.

1. Hypoxia and ischaemia
2. Physical agents
3. chemical agent and drugs.
4. Microbial agents
5. Immunologic agents
6. Nutritional derangements
7. Ageing
8. Psychogenic diseases
9. Iatrogenic Factor
10. Idiopathic disease

I. Hypoxia and ischaemia - Deficiency of oxygen and Hypoxia result in failure to carry out these activities by the cells. Hypoxia is the most common cause of cell injury.

II. Physical agents -

- Mechanical Trauma (eg - road accident)
- thermal Trauma (eg - heat and cold)
- radiation (eg - ultraviolet and ionising)

III. chemical and drugs.

- chemical poisoning such as cyanide, arsenic, mercury.
- environment pollutants
- Social agents such as alcohol and narcotic drugs.

IV Microbial agents -

Injuries by Microbes include infection caused by Bacteria, virus, fungus, protozoa and parasites.

V Immunologic agents

- Hypersensitivity rxn
- autoimmune disease.

VI Nutritional derangements

A deficiency or an excess of nutrients may result in nutritional imbalances.

- starvation

VII Ageing

Cellular ageing or Senescence leads to impaired ability of the cells to undergo replication and repair.

VIII Psychogenic disease.

Morphological changes in common acquired Mental disease due to Mental stress, strain, overwork and Frustration.

ex - depression, schizophrenia

IX Iatrogenic causes

Include occurrence of disease or death to error of Judgment by physician and untoward effect of administered therapy (drugs, radiation)

X Idiopathic disease - It means unknown disease eg - hypertension.

3. PATHOGENESIS OF CELL INJURY

General principles of pathogenesis

1. Type, duration and severity of injurious agents
2. Type, status and adaptability of target cell.
3. Underlying intracellular phenomena
eg - Mitochondrial damage, cell wall damage
4. Morphological consequences
eg - structural changes and swelling.

Points

1. Factor pertaining to etiologic agent and host.
2. Common underlying mechanism.
3. Usual Morphologic changes.
4. Functional implication and disease outcome.

4. REVERSIBLE CELL INJURY.

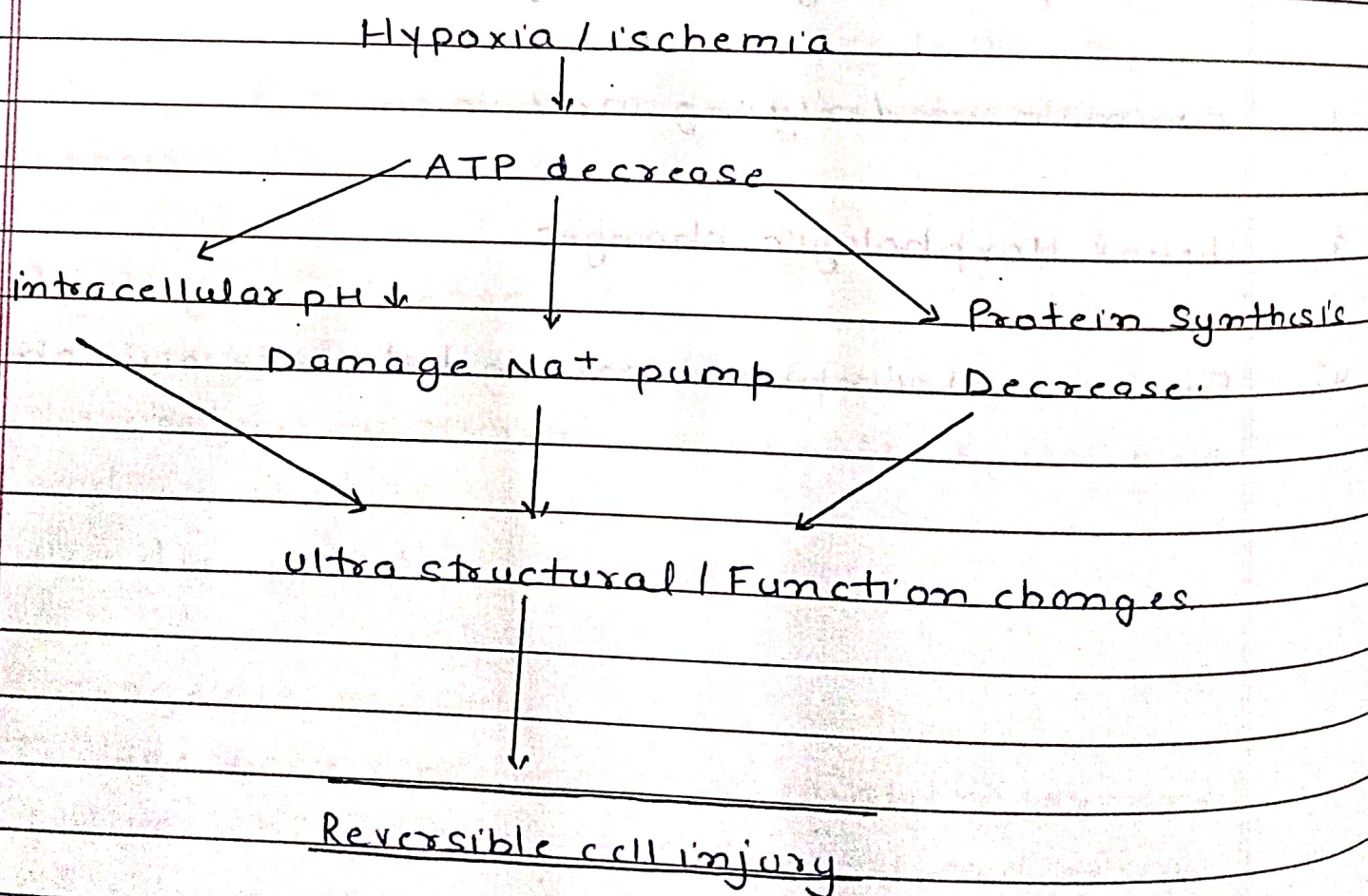
Hypoxia / ischaemia यह दोनो Medical condition है जिसके वजह से ATP decrease हो जाता है।

जब ATP decrease होता है तो यह तीन Problem पैदा कर देता है।

1. Intracellular pH decrease
2. Damage Na⁺ pump
3. Protein Synthesis decrease

इन तीनों changes के कारण ultrastructural / Functional changes आ जाते हैं। इस वजह से Reversible cell injury होता है।

FLOW CHART



- If the hypoxia and ischemia is of short duration the effects are reversible on rapid restoration of blood circulation.

Ex - coronary artery occlusion.

- Note - A coronary occlusion is the partial or complete obstruction of blood flow in coronary artery. The condition may cause a heart attack.

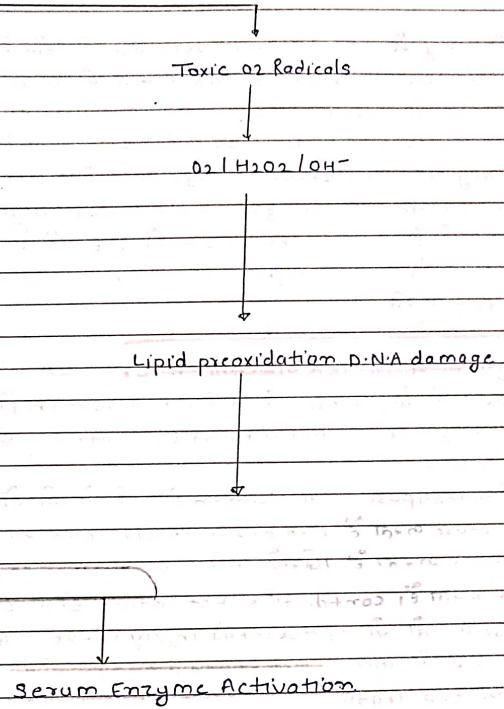
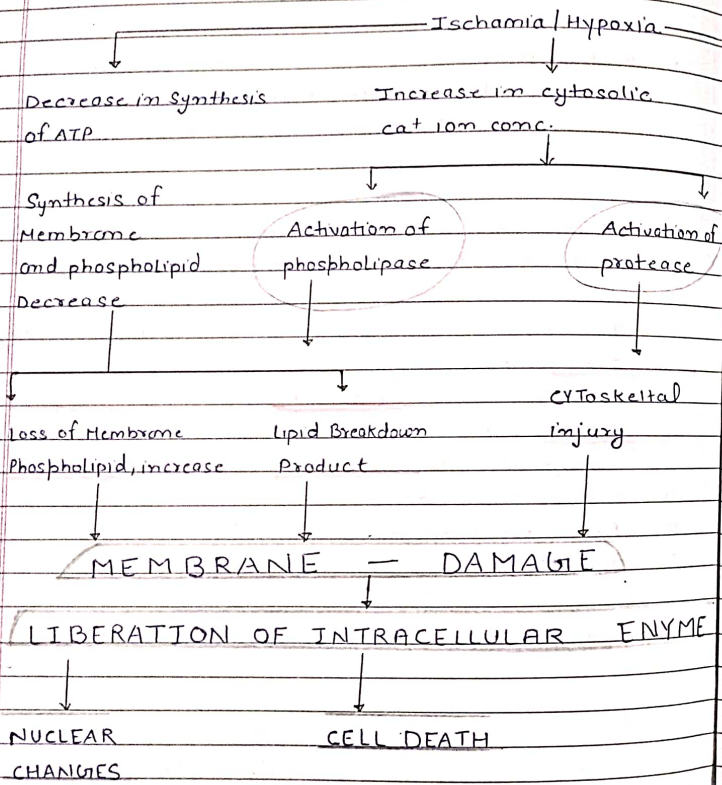
- The metabolism and ultrastructure are reversed if the circulation is quickly restored.

- The sequential changes in reversible cell injury are as following.

- A. Decrease in cellular ATP
- B. Reduced intracellular pH
- C. Damage to plasma membrane Na^+ pump.
- D. Reduce protein synthesis
- E. Functional changes (consequences)
- F. Ultrastructural changes

5. IRREVERSIBLE CELL INJURY

FLOW CHART



→ Ischemia और Hypoxia हमारी Body में काफी समय तक रहे जाते हैं तो तीन Problem occur होते हैं। Ischemia की वजह Toxic O_2 radicals पैदा होते हैं। हमारी Body में ATP बनना Decrease हो जाता है। Cytosol में अंदर cation का concentration ज्यादा हो जाता है।

- तो हमारी Body में ATP का बनना Decrease हो जाने के कारण Membrane or Phospholipid कम हो जाता है। इसके कारण दो Problem पैदा हो जाती हैं - Membrane में Phospholipid का Loss बढ़ता ही चला जाता है। Ultimately यह Membrane damage करते हैं। एक बार Membrane damage हुआ intracellular cellular enzyme होते हैं उनका Liberation होता है जो कि Cell death, Nuclear changes और Serum enzyme Activation करते हैं।

- जब Cytosol में cation का concentration बढ़ जाता है उसके वजह से दो Problem होते हैं। Activation होता है दो enzymes का (Activation) ① Protease ② Phospholipase.

जब Phospholipase का Activation होता है तो वो दो Problem cause करता है Membrane Phospholipid का Breakdown करता है जिसके कारण Lipid breakdown product बनता है। contd. और Activation होता है Protease का तो वो Cytoskeletal injury cause करता है। इन सब के कारण Membrane damage होता है Then cell death.

- Ischemia जब लंबे समय तक रहे जाता है तो Toxic O_2 radicals O_2 हम $2O_2$ यह Lipid Peroxidation करते हैं DNA को Damage करते हैं। Finally Membrane damage करता है Then cell death, Nuclear change और Serum enzyme

- As we know that if the hypoxia and ischemia is of short duration, the effect that are caused by them are reversible on rapid resoration of circulation but if the ischemia and hypoxia persists for longer duration, they tends to cause irreversible change in the structure and function of cell and subsequently leads to cell death.

- Pathogenesis of irreversible cell injury.

When the hypoxia and ischemia persist for long duration they tends to cause mitochondria dysfunction as a result Membrane changes damage occur the finally result liberation of intracellular enzymes that are responsible to the cell death.

So lets discuss about each and every point / stages that are given below, So as to understand the pathogenesis of cell injury.

1. Mitochondria dysfunction
2. Membrane damage
3. Hydrolytic enzyme

• MITOCHONDRIAL DYSFUNCTION

- When the hypoxia persists for long duration, they leads in the production of a large cytosolic influx of calcium ion.
- The calcium ion that had occurred because of the hypoxia, is taken up by the Mitochondria and because of the Mitochondrial dysfunction.
- In other word production of ATP^{BY} Mitochondria decreases.

• MEMBRANE DAMAGE

- Defect in membrane function is most important event in irreversible injury
- The mechanism by which the membrane gets damage are listed below.
 1. Accelerated degradation of membrane phospholipid
 2. Cytoskeletal damage
 3. Toxic oxygen radical
 4. Breakdown product of lipid.

• HYDROLYTIC ENZYME

- Damage to lysosomal Membrane is followed by Liberation of hydrolytic enzymes like ribonuclease, deoxyribonuclease, glycosidase, phosphatases.
- Once when this hydrolytic enzyme are activated, they start digesting the cellular component and induces nuclear changes.

6. DIFFERENCE B/W CELL INJURY

REVERSIBLE

1. A type of cell injury that can return to the steady state by altering cellular condition
2. Can return to the normal position
3. Sub-lethal or mild short acting
4. Caused by lack of oxygen (hypoxia or ischaemia) or blood flow to the cells
5. Result to cellular Swelling and Fat accumulation.
6. Can be treated with drugs.

IRREVERSIBLE

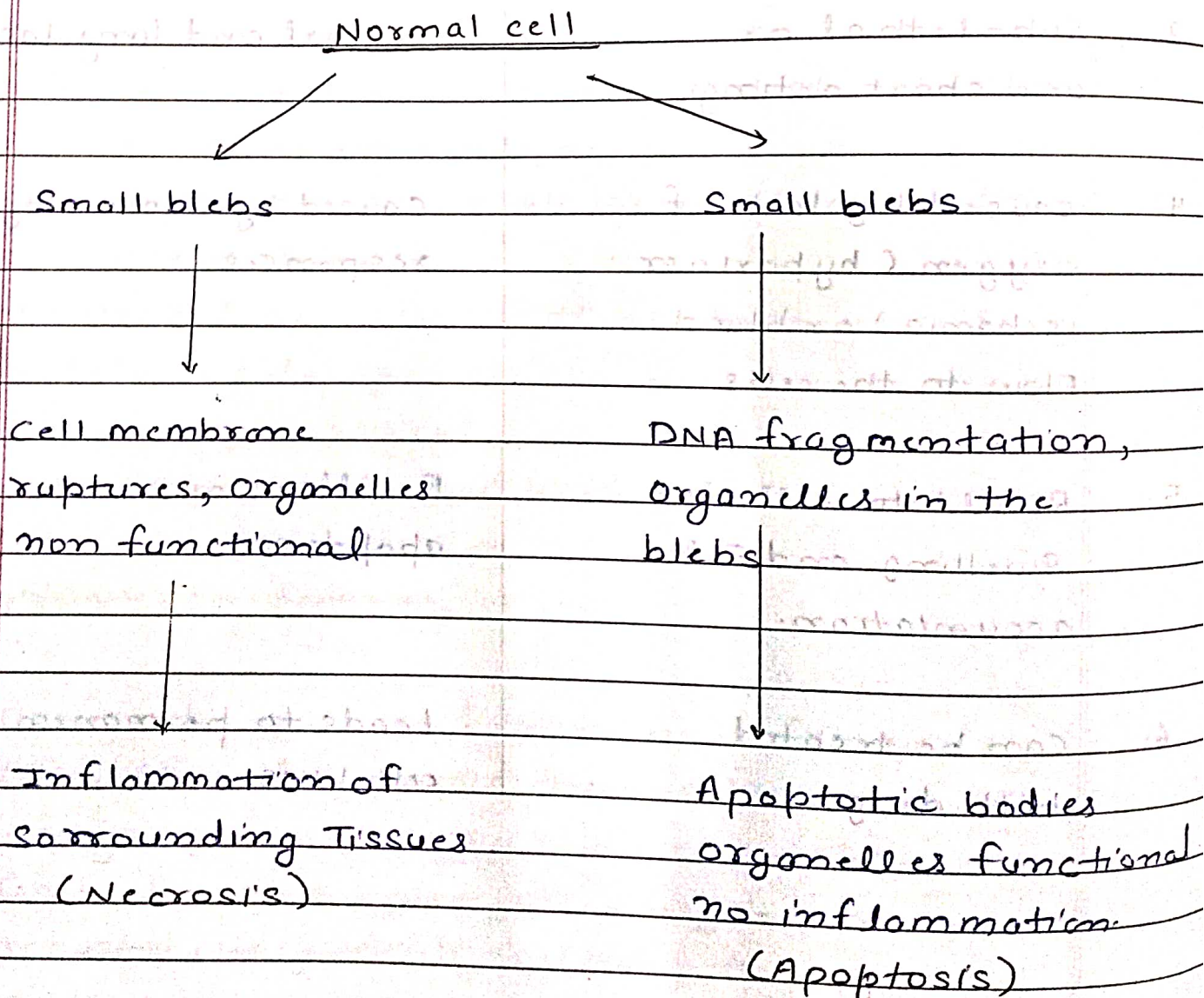
1. One of the severe type of cell injury which lead to the cell death.
2. Has passed to the point no return.
3. Lethal and long lasting
4. Caused by immunological responses.
5. Result is necrosis and apoptosis.
6. Leads to permanent cell loss.

7 CELL DEATH

The body is very good at maintaining a constant number of cell. so there has to exist Mechanism For ensuring other cells in the body are removed, when appropriate.

Two Forms -

- Apoptosis - Suicide - programmed cell death
- Necrosis - Killing - Unprogrammed cell death.



A. APOPTOSIS (PROGRAMMED CELL DEATH)

In human body, cell were produced every second by mitosis there is similar number die by apoptosis.

Between 50-70 billion cells die each day in adult

Between 20-30 billion cells die each day in children

Form of cell death, in which a 'suicide' program is activated within the cell leading to

- Fragmentation of the DNA
 - shrinkage of the cytoplasm
 - Membrane changes and cell death without lysis or damage neighboring cells.
- General characteristic of apoptosis

It is normal phenomenon, occurring frequently in a multicellular organism.

A cell that undergoes apoptosis die neatly, without damaging its neighbours. The cell shrinks and condenses

There is no inflammation in apoptosis.

• Importance of apoptosis.

1. Programmed cell death is needed For proper normal development as mitosis is -

Examples -

- The moldiness of the tadpole tail in frog.
- The formation of the fingers and toes of the fetus requires the removal by apoptosis.

2. Programmed cell death is needed to destroy cells that represent a threat to the integrity of the organism -

Examples

- cells with DNA damage
- cancer cells (Uncontrolled proliferated cells.)

• Mechanisms of apoptosis.

1. Extrinsic pathway

Death receptor pathway

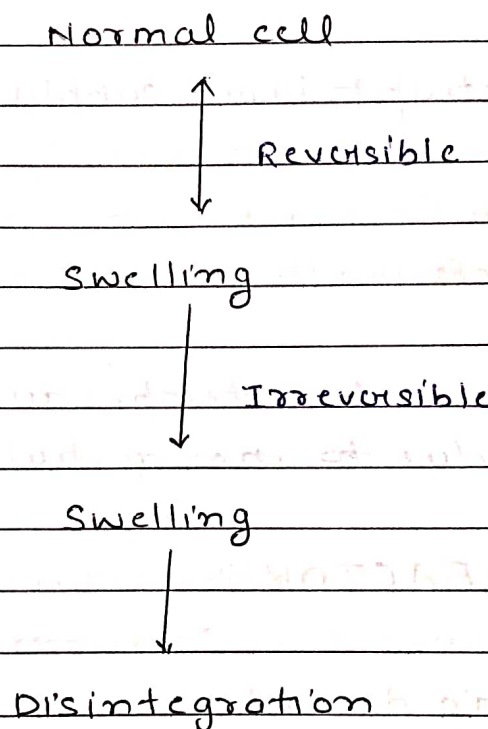
eg - Tumour necrosis Factor

2. Intrinsic pathway

Mitochondrial pathway

B. NECROSIS

- Necrosis is the sum total morphologic changes that follow cell death in a living tissue or organ.
- Dead cells usually show changes in both cytoplasm and in the nucleus.



- Necrosis May occur

- External factor

- Internal Factor

☼ EXTERNAL FACTORS

1. Mechanical Trauma

Physical damage to the body cause cellular breakdown.

2. Damage to blood vessels

which may disrupt blood supply to associated tissue

3. Thermal effects

(Extremely high or low temperature) can result in necrosis due to the disruption of cells.

☼ INTERNAL FACTORS

1. Trophoneurotic disorder

Injury & paralysis of nerve cell.

2. Pancreatic enzyme (lipases)

The Major cause of fat necrosis.

3. Necrosis programs in cells with immunological barriers (intestinal Mucosa) may be alleviate invasion of pathogen through surface affected by inflammation.

4. Bacterial Toxins

Activated natural Killer cell and peritoneal Macrophages.

5. Necrosis programs in cell with immunological barriers (intestinal Mucosa) may alleviate invasion of pathogens through surface affected by inflammation.

6. Toxins and pathogens.

May cause necrosis, toxins such as snake venoms may inhibit enzymes and cause cell death.

✱ MECHANISM OF NECROSIS

NECROTIC CELL DEATH

- Loss of Metabolic function
- Loss of integrity of the cell Membranes
- Cessation of the production of proteins and ATP
- Cells organelles swell and become Non-functional.

1. Depletion of ATP leads
Breakdown of the cell's ion balance
2. Reduce oxygen level
Hypoxia
3. Oxidative stress
The presence of oxygen radicals

✧ SIX TYPES OF NECROSIS

1. Coagulation necrosis
2. Liquefactive necrosis
3. Fat necrosis
4. Caseous Necrosis
5. Gangrenous necrosis
6. Fibrinoid necrosis